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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,481	03/12/2001	David de Graaf	WIBL-P01-523	1227

28120 7590 01/10/2007

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/804,481	GRAAF ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-35,37-46 and 48-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-35, 37-46 and 48-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/17/06 has been entered. Claims 32-35, 37-46 and 48-51 were pending. Applicants amended claims 32, 39, 42 and 49. No claims were added or canceled. Therefore, claims 32-35, 37-46 and 48-51 are pending and examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. The objections to claims 49 and 50 are withdrawn in view of Applicants' amendment to claim 49. The Vidaver et al. rejection under 35 U.S.C. § 102(a) is withdraw in view of Applicants' amendments and/or arguments. The Noonberg et al. rejections under 35 U.S.C. § 103(a) are withdrawn in view of Applicants' amendments and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

3. Claims 32-35, 37-46 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, as

containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicants' claims are directed to a broad genus recombinant vectors (e.g., viral, plasmid, etc.) that can infect host cells of any type (e.g., human, bacterial, yeast, etc.) via any mechanism (e.g., replicate, integrate, etc.). In addition, although said vectors must contain one or more recognition sites for a restriction enzyme, no limitation is placed on the type of restriction enzyme that may be used (e.g., class I, class II, class IIs, class III, etc.).

In contrast, Applicants' specification provides only one example of a pSP-luc+ plasmid contains U1 and a Bae1 "double cleavage" restriction site i.e., a Bae1/U1 construct (e.g., see figure 4; see also Example on pages 21-23).

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). The "written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams formulas, etc., that fully set forth the claimed invention" (e.g., see *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966). Furthermore, adequate disclosure, like enablement, requires representative species, which provide reasonable assurance to one skilled in the art that that applicant

had possession of the ***full scope*** of the claimed invention (e.g., see *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05; see also see *In re Fisher*, 166 USPQ 18 (CCPA 1970)) ("... what the Applicants have actually made and tested [must] reasonably correlate with the scope of the amended claims").

In the present case, Applicants' specification discloses only one example of the claimed genus of recombinant vectors, the Bae1/U1 construct, which is not "representative" of this enormous genus (see above). For example, Applicants fail list representative recombinant vectors (e.g., viral, plasmid, etc.) that can infect representative host cells (e.g., human, bacterial, yeast, etc.) or any representative species of mechanism (e.g., replicate, integrate, etc.). In addition, the specification fails to provide support for the use of "single cleavage" restriction sites or "more than one" recognition sites (e.g., no "single cleavage" species are listed). For example, the recognition site may be removed of "two" single cleavage restriction sites are incorporated into the vector (i.e., at least one would be removed assuming the endonuclease does not cut within the recognition site itself). In addition, Applicants' claims explicitly encompass this possibility with the "one or more recognition sites" limitation (e.g., "two" single cleavage sites).

Furthermore, Applicants claims encompass the use of Type I and Type III

endonucleases where, in contrast to type II enzymes, there is no "strict control" over the cut site (e.g., see Brown, T. A. Genomes. New York: Wiley, Inc. **1999**, pages 30, "There are three types of restriction endonuclease. With Types I and III there is no strict control over the position of the cut relative to the recognition sequence, but with Type II enzymes the cut is always at the same place, either within the recognition sequence or very close to it"). Therefore, Applicants cannot be in possession of a genus of vectors produced by Type. I/III endonucleases because they cannot predict with certainty where these enzymes will cut as exemplified by Brown.

In addition, a person of skill in the art would not expect a "single cleavage" enzyme to excise a restriction fragment that includes the recognition site especially if that enzyme cleaves within its own recognition site (e.g., many enzymes like BamHI, which cleaves G↓GATCC see below, would destroy the recognition site). Although the specificity of a restriction enzyme may be changed by mutation and/or judicious selection of reaction conditions (e.g., see George et al., abstract wherein the recognition of BamHI could be "relaxed" by altering the reaction conditions; see also Lanio et al., Table I wherein mutations in EcoRV caused changes in the substrate specificity), no such "relaxation" has been described in Applicants' specification, nor has an alternative procedures (e.g., mutation) been suggested that might otherwise alter the enzymes recognition and/or cleavage sites. Moreover, it is unclear how multiple recognition sites can produce "a" single restriction fragment. Ten BaeI recognition sites, for instance, would produce twenty cuts in the modified nucleotide sequence (dual cleavage enzyme), which would lead to twenty fragments. Thus, it would appear that even for Applicants'

most preferred embodiment (i.e., BaeI), only "one" recognition site could be used to produce the single restriction fragment (see 35 U.S.C. 112, second paragraph rejection below).

Thus, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the claimed invention especially with regard to sequences that do not possess a restriction site that can be "double cleavage" restriction site. It is well settled that claiming only a result (e.g., digestion with a single enzyme that excises a restriction fragment which includes a single recognition site and forms insertion sites in said nucleotide sequence) fails to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result, far beyond those means actually discovered or contemplated by the inventor, so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse*, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217 ; *Siegel v. Watson*, 105 U.S. Appl. D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119.

Response

4. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] As an initial matter, Applicants reiterate the standards set forth in the written description guidelines and note that they have amended independent claims 32 and 42 (e.g., see 7/17/06 Response, pages 6 and 7). In addition, Applicants argue, "One of skill in the art would know that the inventive portion of the claimed recombinant vector lies in the unique merging of technological features known in the art. For example, digestion with a single restriction enzyme excises from said vector a restriction fragment which includes said recognition site and forms insertion sites in said vector. As the specification sufficiently describes these characteristics of the genus of the claimed recombinant vectors of the invention (see, e.g., page 15, lines 13-29; page 16, lines 1-26; Example on pages 21-23), a skilled artisan would recognize that Applicants were in possession of the claimed invention." (e.g., see 7/17/06 Response, page 7, paragraph 2).

[1] Applicants' arguments are not commensurate in scope with the claims. The claims are not limited to the use of "double restriction" enzymes that cleave outside of their recognition sites like BaeI. For example, Applicants' claims encompass the use of Type I/III endonucleases, which have unpredictable cleavage sites (e.g., see newly amended rejection above). Therefore, Applicants are not in possession of the full scope of the invention.

[2] Applicants further argue, "that at the time this application was filed, snRNAs and vectors for encoding nucleotide sequences such as snRNAs were known and understood. In accordance with the written description guidelines and the MPEP, "[I]nformation which is well known in the art need not be described in detail in the

specification." Written Description Guidelines" (e.g., see 7/17/06 Response, page 7, paragraph 3).

[2] As an initial matter, the Examiner notes that Applicants failed to address any of he evidence set forth by the examiner George et al., Lanio et al., etc. and that mere attorney argument to not rise to the level of factual evidence. See MPEP § 716.01(c): The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). In addition, the Examiner notes that when there is little to no disclosure in the instant specification of the starting material or conditions under which claimed process can be carried out, this failure cannot be rectified by asserting that all disclosure related to the process is within skill of art. Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 (3/13/1997). Here, Applicants do not disclose anything other than BaeI. However, Type I, II, IIs, III and even "relaxed" forms of the enzyme fall within the scope of their claims. As shown by George et al., Lanio et al., and Brown, the art with regard to these other enzymes is inherently unpredictable. A person of skill in the art cannot reliably predict where the Type I/III enzymes will cut (e.g., see Brown above). Furthermore, Applicants' specification provide no guidance to alter or "relax" enzymes to make the type of cuts specified in the claims. Therefore, Applicants' were not in possession of the claimed invention.

Accordingly, the written description rejection cited above is hereby maintained.

New Rejections

Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 32-35, 37-46 and 48-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 32**, the phrase "wherein said nucleotide sequence has been modified to contain one or more recognition sites for a restriction enzyme, such that digestion with a single restriction enzyme excises from said vector a restriction fragment" is vague and indefinite because it is unclear how multiple recognition sites can produce "a" single restriction fragment. Ten BaeI recognition sites, for instance, would produce twenty cuts in the modified nucleotide sequence (dual cleavage enzyme), which would lead to twenty fragments. Thus, it would appear that even for Applicants' most preferred embodiment (i.e., BaeI), only "one" recognition site could be used to produce the single restriction fragment. Therefore, claims 32 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

B. For **claim 42**, the phrase "A recombinant vector comprising an isolated nucleotide sequence encoding an snRNA, wherein said nucleotide sequence comprises an insertion cassette between two insertion sites," is vague and indefinite. For example, it is unclear how "A" single recombinant vector can contain a "cassette"? A cassette contains multiple sequences and, as a result, only a "library" of sequences can contain such a

limitation. Applicants are requested to clarify and/or correct. Therefore, claims 42 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 32-35, 37-46 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for X, does not reasonably provide enablement for Y. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: Applicants' claims are directed to a broad genus recombinant vectors (e.g., viral, plasmid, etc.) that can infect host cells of any type (e.g., human, bacterial, yeast, etc.) via any mechanism (e.g., replicate, integrate, etc.). In addition, although said vectors must contain one or more recognition sites for a restriction enzyme, no limitation is placed on the type of restriction enzyme that may be used (e.g., class I, class II, class IIs, class III, etc.). Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: Applicants claims encompass the use of Type I and Type III endonucleases that are inherently unpredictable to work with since there is no "strict control" over the cut site (e.g., see Brown, T. A. Genomes. New York: Wiley, Inc. 1999, pages 30, "There are three types of restriction endonuclease. With Types I and III there is no strict control over the position of the cut relative to the recognition sequence, but with Type II enzymes the cut is always at the same place, either within the recognition sequence or very close to it"). In addition, a person of skill in the art would not expect a "single cleavage" enzyme to excise a restriction fragment that includes the recognition site especially if that enzyme cleaves within its own recognition site (e.g., many enzymes like BamHI, which cleaves G↓GATCC see below, would destroy the recognition site). Although the specificity of a restriction enzyme may be changed by mutation and/or judicious selection of reaction conditions (e.g., see George et al., abstract wherein the recognition of BamHI could be "relaxed" by altering the reaction conditions; see also Lanio et al., Table I wherein

mutations in EcoRV caused changes in the substrate specificity), no such "relaxation" has been described in Applicants' specification, nor has an alternative procedures (e.g., mutation) been suggested that might otherwise alter the enzymes recognition and/or cleavage sites. Moreover, it is unclear how multiple recognition sites can produce "a" single restriction fragment. Ten BaeI recognition sites, for instance, would produce twenty cuts in the modified nucleotide sequence (dual cleavage enzyme), which would lead to twenty fragments. Thus, it would appear that even for Applicants' most preferred embodiment (i.e., BaeI), only "one" recognition site could be used to produce the single restriction fragment (see 35 U.S.C. 112, second paragraph rejection above).

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants' specification provides only one example of a pSP-luc+ plasmid contains U1 and a Bae1 "double cleavage" restriction site i.e., a Bae1/U1 construct (e.g., see figure 4; see also Example on pages 21-23).

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445

* n.23 (Fed. Cir. 19991).

Claims Rejections - 35 U.S.C. 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 32-34, 37-46 and 48-51 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Verhasselt et al. (Verhasselt et al., "Sequence Analysis of a 37·6 kbp Cosmid Clone from the Right Arm of Saccharomyces

cerevisiae Chromosome XII" *Yeast* **1998**, *13*, 241–250) as evidenced by Sears et al. (Sears et al. "BaeI, another unusual BcgI-like restriction endonuclease" *Nucleic Acids Research* **1996**, *24*, 18, 3590-3592) and Genomenet (Genomenet, Database: EMBL-today Entry: X89514. Retrieved from http://www.genome.jp/dbget-bin/www_bget?embl-today+X89514 on 12/22/06, pages 1-17).

For ***claim 32***, Verhasselt et al. (see entire document) disclose a 37.6 kbp cosmid vector from the right arm of saccharomyces cerevisiae chromosome XII carrying snR6 (see title and abstract), which anticipates the claimed invention. For example, Verhasselt et al. disclose a recombinant vector (e.g., see figure 1 showing "cosmid" cloning vector) comprising an isolated nucleotide sequence encoding an snRNA (e.g., see title wherein snR6 is disclosed; see also page 246, column 1, paragraph 1) wherein said nucleotide sequence has been modified to contain one or more recognition sites for a restriction enzyme such that digestion with a single restriction enzyme excises from said vector a restriction fragment which includes said recognition site and forms insertion sites in said vector (e.g., see Verhasselt et al., figure 1, see also abstract disclosing X89514 accession number for 37.6 kbp cosmid; see also Genomenet, page 9 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 5864-5874 wherein Y = C and NNNN = CCAG at positions ; see also Sears, abstract disclosing the ACNNNNGTAYC binding motif for BaeI). Furthermore, according to Sears et al., restriction with a BaeI enzyme would cleave 10/15 and 12/7 residues to each side of the ACNNNNGTAYC recognition site thus releasing the recognition site upon cleavage by a single enzyme.

The 37.6 kbp cosmid disclosed by Verhasselt et al. meet all of the structural

limitations of the claimed product (see above) except for the product-by-process limitations (i.e., the "digesting" method step) and thus would either anticipate or render obvious the claimed library. See MPEP § 2113, "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)." Here, Applicants' claims are drawn to a recombinant vector (i.e., a product), but are defined by various method steps (i.e., digestion method steps) that distinguish said vector from other vectors and, as a result, represent product-by-process claims. Thus, the process limitations do not appear to provide any patentable weight to the claimed invention in accordance with MPEP § 2113. One of ordinary skill would expect the product to be the same no matter how it was synthesized and/or prepared.

Alternatively, that this limitation is inherently disclosed. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the

burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Here, the 37.6 kbp cosmid contains a BaeI recognition sequence and thus should release the BaeI recognition site upon cleavage with only a single enzyme because BaeI cleaves on both sides of the recognition site as evidenced by Sears et al. (e.g., see Sears et al., abstract).

For ***claims 33 and 34***, Verhasselt et al. disclose U6 snRNA (e.g., see paragraph bridging pages 243 and 246, "The 37 649 kbp contain … the SNR6 gene for the small nuclear RNA U6").

For ***claim 37***, Verhasselt et al. disclose a nucleotide sequence that contains two recognition sites that are identical (e.g., see Genomemet, page 11, positions 15415-15425 wherein another identical ACNNNNGTAYC site is disclosed).

For ***claims 38 and 39***, Verhasselt et al. disclose the ACNNNNGTAYC binding motif for the BaeI restriction enzyme (e.g., see Verhasselt et al., figure 1, see also abstract disclosing X89514 accession number for 37.6 kbp cosmid; see also Genomenet, page 9 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 5864-5874 wherein Y = C and NNNN = CCAG at positions; see also Sears, abstract disclosing the ACNNNNGTAYC binding motif for BaeI).

For ***claim 40***, Verhasselt et al. disclose, for example, insertion sites that "comprise" the complement of SEQ ID NO 2 (i.e., CGTCC) and SEQ ID NO 3 (i.e.,

ACTCT) at positions 11749-11753 and 1046-1050 (e.g., see Genomenet, pages 10 and 8), respectively.

For ***claim 41***, Verhasselt et al. do not explicitly state that digestion with BaeI would excise a double stranded restriction fragment with single stranded overhangs, but the Examiner contends that this would be an inherent property of the ACNNNNGTAYC sequence disclosed by Verhasselt et al. (see above) because BaeI produces "3' overhangs" as evidenced by Sears et al. (e.g., see top of figure 3). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 42***, Verhasselt et al. disclose a recombinant vector comprising an isolated nucleotide sequence encoding an snRNA (e.g., see above wherein U6 snRNA is disclosed) wherein said nucleotide sequence comprises an insertion cassette between two insertion sites (e.g., see Verhasselt et al., abstract wherein 25 open reading frames are disclosed between two "flanking" cosmid insertion sites). The method limitation to form by digestion with a single restriction enzyme to excise from said vector a restriction fragment that contains a recognition site for said restriction enzyme and wherein said insertion cassette comprises a modification fragment comprising a nucleotide sequence

complementary to a target" has not been afforded any patentable weight because as noted above "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. See MPEP § 2113. Here, an enzyme like BaeI would not impart any "structural difference" to the sequence because it cleaves 10/15 and 12/7 nucleotides from the ACNNNNGTAYC sequence. Thus, "any" sequence could be produced by this cut because the cut does not depend on the identity of the nucleotides 10/15 and 12/7 nucleotides away from the 5' and 3' ends of the ACNNNNGTAYC sequence. Likewise, the identity of the modification fragment also encompasses "any" sequence because.the target to which it binds has not been specified. In addition, the metes and bound of the claimed invention cannot be determined because it is unclear what constitutes a cassette (e.g., see 35 U.S.C. 112, second paragraph rejection above).

For ***claims 43-45***, Verhasselt et al. disclose U6 snRNA (e.g., see paragraph bridging pages 243 and 246, "The 37 649 kbp contain … the SNR6 gene for the small nuclear RNA U6").

For ***claims 46, 48***, Verhasselt et al. disclose an insertion cassette comprises a modification fragment of about 30 base pairs of DNA (e.g., any 30 bp segment of the 36 639 bp cosmid clone qualifies, see above). Furthermore, the cosmid clone is double stranded, which reads on claim 48.

For ***claim 49***, Verhasselt et al. disclose the ACNNNNGTAYC binding motif for the BaeI restriction enzyme (e.g., see Verhasselt et al., figure 1, see also abstract

disclosing X89514 accession number for 37.6 kbp cosmid; see also Genomenet, page 9 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 5864-5874 wherein Y = C and NNNN = CCAG at positions; see also Sears, abstract disclosing the ACNNNNGTAYC binding motif for BaeI).

For ***claim 50***, Verhasselt et al. disclose, for example, insertion sites that "comprise" the complement of SEQ ID NO 2 (i.e., CGTCC) and SEQ ID NO 3 (i.e., ACTCT) at positions 11749-11753 and 1046-1050 (e.g., see Genomenet, pages 10 and 8), respectively.

For ***claim 51***, Verhasselt et al. do not explicitly state that digestion with BaeI would excise a double stranded restriction fragment with single stranded overhangs, but the Examiner contends that this would be an inherent property of the ACNNNNGTAYC sequence disclosed by Verhasselt et al. (see above) because BaeI produces "3' overhangs" as evidenced by Sears et al. (e.g., see top of figure 3). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

10. Claims 32-35, 38-46 and 48-51 are rejected under 35 U.S.C. 102(b) as being anticipated

by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shambaugh et al. (Shambaugh et al., "The splicesomal U small nuclear RNAs of Ascaris lumbricoides" *Molecular and Biochemical Parasitology* **1994**, *64*, 349-352) as evidenced by Sears et al. (Sears et al. "Bael, another unusual BcgI-like restriction endonuclease" Nucleic Acids Research 1996, **24**, 18, 3590-3592) and NCBI (NCBI, Entry: L22246. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nucleotide&val=L22246 on 12/23/06, pages 1-3).

For ***claim 32***; Shambaugh et al. (see entire document) disclose a 6 kb restrict fragment containing four U1 genes (see Shambaugh et al., page 350, column 1, first full paragraph; see also figure 1; see also page 349, Note at bottom disclosing L22246 accession number), which anticipates the claimed invention. For example, Shambaugh et al. disclose a recombinant vector (e.g., see page 350, column 1, first full paragraph) comprising an isolated nucleotide sequence encoding an snRNA (e.g., see page 350, column 1, first full paragraph wherein U1 snRNA is disclosed; see also NCBI, page 1) wherein said nucleotide sequence has been modified to contain one or more recognition sites for a restriction enzyme such that digestion with a single restriction enzyme excises from said vector a restriction fragment which includes said recognition site and forms insertion sites in said vector (e.g., see Shambaugh et al., page 349, disclosing L22246 accession number; see also NCBI, page 2 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 348-358 wherein Y = C and NNNN = CGCC at positions; see also Sears, abstract disclosing the ACNNNNGTAYC binding motif for BaeI). Furthermore, according to Sears et al., restriction with a BaeI enzyme would

cleave 10/15 and 12/7 residues to each side of the ACNNNNGTAYC recognition site thus releasing the recognition site upon cleavage by a single enzyme.

The L22246 clone meets all of the structural limitations of the claimed product (see above) except for the product-by-process limitations (i.e., the "digesting" method step) and thus would either anticipate or render obvious the claimed library. See MPEP § 2113, "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)." Here, Applicants' claims are drawn to a recombinant vector (i.e., a product), but are defined by various method steps (i.e., digestion method steps) that distinguish said vector from other vectors and, as a result, represent product-by-process claims. Thus, the process limitations do not appear to provide any patentable weight to the claimed invention in accordance with MPEP § 2113. One of ordinary skill would expect the product to be the same no matter how it was synthesized and/or prepared.

Alternatively, that this limitation is inherently disclosed. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). "When the PTO shows a sound basis for believing that the products of the applicant and

the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Here, the L22246 clone contains a BaeI recognition sequence and thus should release the BaeI recognition site upon cleavage with only a single enzyme because BaeI cleaves on both sides of the recognition site as evidenced by Sears et al. (e.g., see Sears et al., abstract).

For ***claims 33 and 34***, Shambaugh et al. disclose U1 snRNA (e.g., see page 350, column 1, first full paragraph; see also NCBI, page 1).

For ***claim 35***, Shambaugh et al. disclose a vector wherein the snRNA is U1 and wherein said nucleotide sequence has been modified within the first 11 nucleotides of the coding region (e.g., see NCBI, page 1 wherein four U1 snRNAs are disclosed with different modification in the first 11 nucleotides of the coding region at positions 2071-2236, 3195-3358, 4551-4715, and 5535-5700. As noted above, "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. See MPEP § 2113. Here, any U1 snRNA represents a "modification" relative to the other snRNAs because they do not share the same sequences. Any "method steps" for making a modification are not afforded any

patentable weight in accordance with MPEP § 2113 because Applicants are not claiming a method but, rather, a product and "the patentability of a product does not depend on its method of production" as noted above.

For ***claims 38 and 39***, Shambaugh et al. disclose the ACNNNNGTAYC binding motif for the BaeI restriction enzyme (e.g., see Shambaugh et al., page 349, disclosing, L22246; see also NCBI, page 2 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 348-358 wherein Y = C and NNNN = CGCC at positions; see also Sears et al., abstract disclosing the ACNNNNGTAYC binding motif for BaeI).

For ***claim 40***, Shambaugh et al. disclose, for example, insertion sites that "comprise" the complement of SEQ ID NO 2 (i.e., CGTCC) and SEQ ID NO 3 (i.e., ACTCT) at positions 3340-3344 and 4343-4347 (e.g., see NCBI, 2 and 3), respectively.

For ***claim 41***, Shambaugh et al. do not explicitly state that digestion with BaeI would excise a double stranded restriction fragment with single stranded overhangs, but the Examiner contends that this would be an inherent property of the ACNNNNGTAYC sequence disclosed by Shambaugh et al. (see above) because BaeI produces "3' overhangs" as evidenced by Sears et al. (e.g., see top of figure 3). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977)

and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 42***, Shambaugh et al. disclose a recombinant vector comprising an isolated nucleotide sequence encoding an snRNA (e.g., see above wherein U6 snRNA is disclosed) wherein said nucleotide sequence comprises an insertion cassette between two insertion sites (e.g., see Shambaugh et al., page 350, column 1, first full paragraph wherein any and/or all of the U1 genes represent the insertion cassette i.e., the whole 6 kb is a restriction fragment). The method limitation to form by "digestion with a single restriction enzyme to excise from said vector å restriction fragment that contains a recognition site for said restriction enzyme and wherein said insertion cassette comprises a modification fragment comprising a nucleotide sequence complementary to a target" has not been afforded any patentable weight because as noted above "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself." The patentability of a product does not depend on its method of production. See MPEP § 2113. Here, an enzyme like BaeI would not impart any "structural difference" to the sequence because it cleaves 10/15 and 12/7 nucleotides from the ACNNNNGTAYC sequence. Thus, "any" sequence could be produced by this cut because the cut does not depend on the identity of the nucleotides 10/15 and 12/7 nucleotides away from the 5' and 3' ends of the ACNNNNGTAYC sequence. Likewise, the identity of the modification fragment also encompasses "any" sequence because the target to which it binds has not been specified. In addition, the metes and bound of the claimed invention cannot be determined because it is unclear what constitutes a cassette (e.g., see 35 U.S.C. 112, second paragraph rejection above).

For ***claims 43-45***, Shambaugh et al. disclose U1 snRNA (e.g., see page 350, column 1, first full paragraph; see also NCBI accession L22246).

For ***claims 46, 48***, Shambaugh et al. disclose an insertion cassette comprises a modification fragment of about 30 base pairs of DNA (e.g., see figure 1 wherein any 30 bp segment qualifies, see above; see also NCBI, wherein any 30 base pair segment qualifies). Furthermore, note that 6 kb restrict fragment is double stranded, which reads on claim 48.

For ***claim 49***, Shambaugh et al. disclose the ACNNNNGTAYC binding motif for the BaeI restriction enzyme (e.g., see page 349, disclosing, L22246; see also NCBI, page 2 wherein the BaeI recognition site ACNNNNGTAYC is disclosed at positions 348-358 wherein Y = C and NNNN = CGCC at positions; see also Sears et al., abstract disclosing the ACNNNNGTAYC binding motif for BaeI).

For ***claim 50***, Shambaugh et al. disclose, for example, insertion sites that "comprise" the complement of SEQ ID NO 2 (i.e., CGTCC) and SEQ ID NO 3 (i.e., ACTCT) at positions 3340-3344 and 4343-4347 (e.g., see NCBI, 2 and 3), respectively.

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same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01. The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
December 23, 2006

JON EPPERSON
PRIMARY EXAMINER